Gender Differences in Hematopoietic and Lymphoproliferative Disorders and Other Cancer Risks by Major Occupational Group Among Workers Exposed to Benzene in China

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Gender differences in risk for leukemia and other selected and combined disease categories were examined by major occupational category for 74,828 benzene-exposed workers compared to 35,805 unexposed workers from 12 cities in China. No significant differences in the relative risks for total

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Benzene is an important chemical product, or intermediate, a natural constituent of crude oil, an indirect product of industrial processes (coke ovens), and a contaminant of several important solvents.[1] Although the association of benzene with leukemia has been known for more than 60 years[2] and internationally recognized since 1981,[1] the key studies[3–5] have usually focused on mortality outcomes in a single occupational or industrial category of male benzene-exposed workers and have generally yielded small numbers of leukemia cases.

To overcome some of these limitations, we carried out a cohort study in 672 factories in 12 cities in China that included approximately 75,000 benzene-exposed workers, nearly half of whom were female, and 35,000 unexposed workers. We have previously reported that malignant neoplasms are the leading cause of death and cardiovascular disorders the second most common condition, together accounting for approximately 75% of all deaths among these benzene workers, and that no significant differences were found between female and male benzene-exposed workers in relative risks for nonmalignant conditions, solid tumors, or hematopoietic and lymphoproliferative (HLP) malignancies (including total leukemia, acute myeloid leukemia [the most common type], and malignant lymphoma).[6] This article presents a standardized

mortality and cancer mortality were found between female and male benzene-exposed workers, although risks tended to be somewhat higher among male than among female employees. Both female and male workers in several occupational categories had notably increased risks for all hematopoietic and lymphoproliferative (HLP) malignant and nonmalignant disorders combined and for total leukemia. Variation in risk for HLP disorders by occupational category was observed in both genders, with highest risks for male and female chemical manufacturing workers, female nonproduction employees, and male printers. However, the numbers of leukemia and other HLP malignancies in each category were small. The findings suggest that both female and male benzene-exposed workers in several occupational categories experience excess leukemia and other HLP disorders with relatively minor gender differences. Although this population is one of the largest cohorts of benzene-exposed workers studied to date, evaluation of the observed variation in risk for HLP neoplasms among the occupational groups for workers of each gender is limited by the small numbers of these relatively rare malignancies.

assessment of leukemia and other cancer risk among male and female benzene-exposed workers according to major occupational categories.

Methods

The methods for this study are described in detail elsewhere.[7,8] Put briefly, the study population consisted of 74,828 benzene-exposed workers, identified from eligible work units in 672 factories, and the comparison population included 35,805 unexposed workers from 109 factories located in 12 cities and surrounding areas in China. Using monthly salary records, field center staff identified all workers employed for any length of time in the eligible factories during 1972–1987 and followed them up through December 31, 1987 or termination, if sooner. If salary records were not available or were incomplete, other written data sources were used in a standardized approach.

Data ascertained for each eligible worker included name, birth date, gender, job history, and vital status as of December 31, 1987. Occurrence of leukemia or other HLP disorder, history of benzene poisoning, and cause of death for deceased workers were obtained from medical records, other written factory records, death certificates at local police stations, or, as a last resort, the worker's physician or next-of-kin. For all suspected cases of leukemia or other HLP disorder, medical records and available pathology slides and peripheral blood smears were requested and reviewed by hematopathologists from the Peking Union Medical College Hospital, the National Cancer Institute, and the Mayo Clinic.[9]

Each exposed worker was classified, based on his/her years of employment, as belonging to one of the following main occupational categories: chemical production, rubber manufacturing, varnish insulation, shoe manufacturing, printing, painting or paint manufacturing, nonproduction activities (including helpers and other nonproduction workers), and a combined category of management/technical/service and cleaning tasks. The last category was initially considered as two groups (managers/technicians and service/cleaning workers), but later combined because of small size and the relatively low and indirect benzene exposures of each group.

Estimates of gender-specific rate ratios and the female-to-male ratio of rate ratios were calculated for several mortality outcomes and for incidence of HLP disorders, comparing all exposed workers in each of the occupational groups to unexposed workers. We used Poisson regression and treated exposure and employment as time-dependent variables.[10,11] The female-to-male rate ratios were obtained from a model that included a gender-by-exposure interaction. Ninety-five percent confidence intervals were obtained from the profile likelihood.[11,12]

Results

Slightly less than half of the exposed workers were women compared to 40% of the unexposed workers (Table 1). Exposed women and men were followed for a median of 10.2 and 12.4 years, respectively, compared with 11.4 and 16.3 years for unexposed women and men (data not shown). Slightly more person-years were contributed by men born before 1930, hired before 1960, or were age 40 or older at the time of hire, whereas, among women, slightly more person-years were contributed by those born in 1950 or more recently, hired after 1972, and were under age 30 at hire (data not shown). Women were more likely than men to have left study work units because of retirement, whereas men were somewhat more likely than women to have left employment because of moving from the 12 cities or because of illness (Table 1).

Although relative risk estimates (RRs) for total mortality were generally slightly higher for men than for women in the corresponding specific occupational categories, no significant gender differences in total mortality were observed, except for helpers, the only category characterized by significantly higher relative risk among women than among men (Table 2). Small increases in relative risks for both men and women were observed among chemical and rubber manufacturing workers and painters and paint manufacturers.

RRs for all cancer deaths combined were also similar among male and female benzene-exposed workers, although generally somewhat higher for men (Table 3). For women, no significant excesses were observed, but rubber manufacturing workers, printers, and helpers had nonsignificantly increased risks compared to unexposed workers. Male painters and paint manufacturing workers had a significant 40% excess, men employed in chemical production and in rubber manufacturing had marginally significant 50–60% increases, and male

TABLE 1
Distribution of Benzene-exposed and Unexposed Workers by Employment Status and Vital Status at End of Follow-up by Gender: Cohort Study of Chinese Benzene Workers, 1972–1987

Status	Exposed						Unexposed					
	Women			Men			Women			Men		
	Number	Person-years	Column %	Number	Person-years	Column %	Number	Person-years	Column %	Number	Person-years	Column %
Employment												
Still working	28,138	257,421	78.2	29,937	291,401	77.1	11,850	122,703	79.0	16,639	190,232	80.0
Retired	5,602	84,669	15.5	5,618	84,623	14.5	2,198	34,568	14.6	2,522	39,417	12.1
Moved from area	1,624	18,742	4.5	2,171	25,482	5.6	727	8,766	4.8	1,088	14,424	5.2
Illness	530	6,855	1.5	748	9,495	1.9	193	2,628	1.3	351	4,836	1.7
Deceased before leaving study factories	102	780	0.3	358	3,028	0.9	42	354	0.3	195	1,594	0.9
Vital status												
Alive	35,677	365,603	99.2	37,635	402,515	97.2	14,873	167,709	99.2	20,244	245,188	97.7
Deceased	273	2,619	0.7	1,096	10,945	2.7	113	1,130	0.9	485	4,833	1.9
Lost to follow-up	46	245	0.1	101	569	0.1	24	180	0.1	66	482	0.2
Total	35,996	368,468	100.0	38,832	414,029	100.0	15,010	169,019	100.0	20,795	250,504	100.0

TABLE 2
Gender Differences in Mortality Risk from All Causes Among Benzene-exposed Workers by Major Occupational Group *v* Unexposed Workers: Cohort Study of Chinese Benzene Workers, 1972–1987

Major Occupational Group	Women			Men			Ratio Women/Men	
	Number of Deaths Exposed/Unexposed	Relative Risk	95% Confidence Interval	Number of Deaths Exposed/Unexposed	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Chemical manufacturers	12/113	1.18	(0.61–2.05)	65/485	1.29	(0.98–1.66)	0.91	(0.46–1.69)
Rubber manufacturers	22/113	1.13	(0.70–1.75)	57/485	1.38	(1.03–1.80)	0.82	(0.47–1.38)
Varnish insulation workers	3/113	0.35	(0.09–0.93)	9/485	0.72	(0.35–1.31)	0.49	(0.11–1.67)
Shoeworkers	8/113	0.38	(0.17–0.73)	222/485	0.93	(0.79–1.10)	0.41	(0.18–0.80)
Printers	1/113	0.62	(0.04–2.77)	9/485	1.06	(0.51–1.93)	0.58	(0.03–3.15)
Painters and paint manufacturers	182/113	1.08	(0.85–1.36)	622/485	1.22	(1.08–1.37)	0.88	(0.68–1.15)
Nonproduction workers	32/113	0.96	(0.64–1.41)	43/485	0.65	(0.47–0.88)	1.48	(0.89–2.44)
Helpers	20/113	1.42	(0.86–2.24)	19/485	0.68	(0.42–1.05)	2.08	(1.07–4.06)
Other nonproduction workers	12/113	0.61	(0.32–1.07)	24/485	0.62	(0.40–0.91)	0.99	(0.46–2.01)
Managers/technicians/service and cleaning workers	12/113	0.76	(0.40–1.32)	81/485	0.97	(0.76–1.22)	0.78	(0.39–1.44)

painters and managers/technicians/service and cleaning workers had nonsignificant increases (Table 3).

Both female and male workers in several occupational categories had notably increased risks for all HLP malignant and nonmalignant disorders combined (Table 4) and for total leukemia (Table 5). Again, gender differences in RRs were not significant. The type of HLP malignancy occurring in excess varied according to occupational group despite the common denominator of benzene exposure. Although leukemia was the most

TABLE 3
Gender Differences in Mortality Risk from All Neoplasms Among Benzene-exposed Workers by Major Occupational Group *v* Unexposed Workers: Cohort Study of Chinese Benzene Workers, 1972–1987

Major Occupational Group	Women			Men			Ratio Women/Men	
	Number of Deaths Exposed/Unexposed	Relative Risk	95% Confidence Interval	Number of Deaths Exposed/Unexposed	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Chemical manufacturers	4/45	0.97	(0.29–2.38)	28/176	1.49	(0.98–2.19)	0.65	(0.18–1.76)
Rubber manufacturers	11/45	1.41	(0.69–2.64)	24/176	1.60	(1.02–2.39)	0.88	(0.39–1.91)
Varnish insulation workers	0/45	0	(0–0.56)	2/176	0.45	(0.75–1.40)	0	(0–2.09)
Shoeworkers	2/45	0.25	(0.04–0.81)	77/176	0.92	(0.70–1.21)	0.27	(0.04–0.92)
Printers	1/45	1.52	(0.09–6.98)	5/176	1.65	(0.59–3.61)	0.92	(0.05–5.92)
Painters and paint manufacturers	62/45	0.97	(0.66–1.43)	250/176	1.39	(1.14–1.69)	0.70	(0.46–1.08)
Nonproduction workers	16/45	1.23	(0.67–2.14)	15/176	0.63	(0.36–1.03)	1.95	(0.89–4.29)
Helpers	9/45	1.59	(0.73–3.10)	6/176	0.59	(0.23–1.23)	2.67	(0.92–8.35)
Other nonproduction workers	7/45	0.95	(0.39–2.00)	9/176	0.65	(0.31–1.20)	1.46	(0.49–4.14)
Managers/technicians/service and cleaning workers	5/45	0.75	(0.26–1.72)	38/176	1.20	(0.83–1.69)	0.62	(0.20–1.55)

TABLE 4
Gender Differences in Incidence Risk from All Hematopoietic and Lymphoproliferative Disorders Among Benzene-exposed Workers by Major Occupational Group *v* Unexposed Workers: Cohort Study of Chinese Benzene Workers, 1972–1987

Major Occupational Group	Women			Men			Ratio Women/Men	
	Number of Deaths Exposed/Unexposed	Relative Risk	95% Confidence Interval	Number of Deaths Exposed/Unexposed	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Chemical manufacturers	2/3	6.52	(0.86–39.44)	8/10	6.50	(2.47–16.59)	1.00	(0.11–7.59)
Rubber manufacturers	2/3	5.09	(0.67–30.96)	3/10	3.68	(0.82–12.04)	1.39	(0.13–13.43)
Varnish insulation workers	0/3	0	(0–13.79)	1/10	3.75	(0.48–29.42)	0	(0–9.65)
Shoeworkers	2/3	3.87	(0.51–23.47)	4/10	1.11	(0.29–3.47)	3.49	(0.35–31.11)
Printers	0/3	0	(0–48.74)	1/10	6.43	(0.35–34.02)	0	(0–19.95)
Painters and paint manufacturers	13/3	3.24	(1.04–14.15)	24/10	2.71	(1.22–5.96)	1.19	(0.30–6.04)
Nonproduction workers	9/3	11.69	(3.48–52.77)	5/10	3.71	(1.16–10.45)	3.15	(0.63–19.84)
Helpers	4/3	10.63	(2.34–54.01)	1/10	1.71	(0.09–8.96)	6.20	(0.63–78.93)
Other nonproduction workers	5/3	12.55	(3.07–61.32)	4/10	5.28	(1.44–15.82)	2.38	(0.40–17.15)
Managers/technicians/service and cleaning workers	0/3	0	(0–5.61)	4/10	2.05	(0.79–7.34)	0	(0–3.53)

TABLE 5
Gender Differences in Incidence Risk from Total Leukemia Among Benzene-exposed Workers by Major Occupational Group v Unexposed Workers: Cohort Study of Chinese Benzene Workers, 1972–1987

Major Occupational Group	Women			Men			Ratio Women/Men	
	Number of Deaths Exposed/Unexposed	Relative Risk	95% Confidence Interval	Number of Deaths Exposed/Unexposed	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
Chemical manufacturers	0/2	0	(0–15.59)	5/7	5.71	(1.82–18.24)	0	(0–3.38)
Rubber manufacturers	1/2	3.59	(0.17–37.90)	1/7	1.78	(0.10–10.01)	2.02	(0.06–71.73)
Varnish insulation workers	0/2	0	(0–22.45)	0/7	0	(—)	0.93	(—)
Shoeworkers	1/2	3.19	(0.15–33.30)	3/7	1.17	(0.24–4.45)	2.73	(0.10–42.89)
Printers	0/2	0	(0–92.50)	0/7	0	(—)	1.00	(—)
Painters and paint manufacturers	6/2	2.14	(0.49–14.68)	15/7	2.43	(1.02–6.00)	0.88	(0.15–7.11)
Nonproduction workers	4/2	7.36	(1.43–53.09)	5/7	5.22	(1.54–16.35)	1.41	(0.19–13.45)
Helpers	2/2	7.88	(0.95–65.75)	1/7	2.45	(0.13–13.79)	3.21	(0.20–97.03)
Other nonproduction workers	2/2	6.71	(0.81–55.93)	4/7	7.35	(1.92–24.43)	0.91	(0.08–10.47)
Managers/technicians/service and cleaning workers	0/2	0	(0–9.59)	2/7	1.47	(0.30–7.21)	0	(0–10.09)

common HLP malignancy elevated among both female and male workers, male varnish and printing workers both had excess non-Hodgkin's lymphoma (no leukemia cases were observed among men or women in these categories) and female chemical and nonproduction workers had elevated aplastic anemia and non-Hodgkin's lymphoma (but only female nonproduction workers also had increased leukemia).

Some (nonsignificant) gender differences in RRs for HLP disorders were suggested, however, including the increased risks for male varnish insulation workers, printers, and managers/technicians/service and cleaning workers, although no cases were found among exposed women in these occupational categories. Conversely, female, but not male, shoeworkers and helpers had elevated risks (Table 4).

Discussion

Women were somewhat more likely to be born later, hired later, to be younger at hire, and to have retired earlier compared to men, but only small gender differences in risk (RRs generally higher among men) were observed for all causes and for all neoplasms in the various occupational categories. RRs for all HLP and total leukemia were markedly elevated among workers in several benzene-exposed occupational groups, with increases generally similarly affecting women and men. Some variation in RRs was seen according to occupational group for workers of both genders, although the numbers of leukemias and other HLP disorders in each category were small. The findings suggest that risk of leukemia or other HLP disorders is increased in certain occupational categories among both women and men, that there may be some variation in risk according to occupational category, and that leukemia is the main, but not only, type of HLP disorder occurring in excess.

Prior research on female benzene-exposed workers or female workers in the major occupational categories included in the present study has been limited. Most of the relevant studies exclude female workers without indicating a reason or because of small numbers, difficulty in tracing, or other explanations. Others report findings but do not indicate the gender of workers described.

Three populations of chemical manufacturing workers,[3,5,13–15] consistently included in reviews and/or risk assessment reports of benzene-exposed workers,[16,17] either do not report the gender of workers or exclude females because of small numbers. Benzene-exposed male chemical workers in the largest cohort had twofold to fourfold elevated risk for specific types of HLP neoplasms, based on 19 HLP cases (seven leukemias).[15] Other reports of chemical production cohorts also exclude consideration of female workers.[18–23] O'Berg et al,[24] however, found a 30% excess for leukemia and a 20% increase for lymphoma among 21,000 women in the chemical production industry, primarily because of higher risks among salary, but not wage, workers.

An excess of HLP malignancies (and several other cancers including bladder, stomach, prostate, and lung neoplasms) has been identified among some groups of rubber workers.[25–36]

One particular subtype of HLP neoplasms, namely lymphatic leukemia, has been linked with various solvent exposures, including carbon disulfide, carbon tetrachloride, ethyl acetate, and benzene.[37–40] Among three reports describing quantitative estimates of risk among American female rubber industry workers, one showed a nonsignificantly elevated mortality risk for all HLP, but no leukemia excess, similar to the findings for white, male, salaried workers.[41] Another found no increase for all HLP, but small, nonsignificant excesses for multiple myeloma and non-Hodgkin's lymphoma among female hourly workers, in contrast to increases among males for all HLP, monocytic leukemia, and other lymphatic disorders.[42] The largest study found no excess for leukemia among union members or salaried workers, but a nonsignificant increase for the combined category of non-Hodgkin's lymphoma and multiple myeloma among salaried white women only, compared with nonsignificant increases of both leukemia and the combined category of non-Hodgkin's lymphoma and multiple myeloma among white, male, union members.[31]

Female workers were either excluded or not specifically mentioned in several studies of printers.[43–48] Excesses of myelomonocytic leukemia[47] and non-Hodgkin's lymphoma[48] were found in proportionate mortality studies of male workers, as were several cases of myelofibrosis.

None of the large occupational cohort studies of painters described numbers or risk estimates for female workers.[49] Nonsignificantly elevated leukemia risks were reported in American proportionate mortality[50] and cohort studies[51,52] and in analyses of nationwide death certificate data from the United States[53] and the United Kingdom.[54] A nonsignificant increase of lymphatic leukemia was described in a large cohort of Swedish painters.[55,56]

As one of the first and largest detailed studies of benzene-exposed workers to assess risk according to gender and occupational group, this study suggests that cancer and nonmalignant disease risk do not differ appreciably between men and women. Our ability to further assess possible variation in risk among the major occupational categories was limited by the relatively small numbers of leukemia and other HLP disorders. Because of the small numbers, we did not further evaluate the occupational category-specific and gender-specific cancer risks by time period, city, or other type of stratification. However, the population experienced a wide spectrum of exposures.[8] It is possible that the differences observed may reflect variation in exposure levels and/or duration among occupational categories comprising the present cohort. These possibilities are currently being assessed in ongoing analyses. Future papers will present gender-specific and adjusted risk estimates for specific and combined HLP disorders and other cancers according to exposure levels and related variables (eg, duration of employment, cumulative exposure, intensity measures), with appropriate consideration of time-related changes.

As women increasingly enter the work force and take on industrial jobs previously held exclusively by men, detailed comparisons in risk by gender will become more common. It is hoped that future studies of female workers exposed to benzene and other chemicals can also include evaluation of health outcomes, in addition to cancer, and detailed investigation of the role of other influences (including hormonal and other physiological influences) on the risk of cancer mortality and incidence.

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